-- 35. **[Amended]** The array of claim 34, wherein the modified oligonucleotides further comprise an end block at the 3' end and exhibit exonuclease resistance of at least twice that of a naturally occurring oligonucleotide having the same number of residues. --

-- 36. **[Amended]** The array of claim 34, wherein the modified oligonucleotides further comprise an end block at the 5' end and exhibit exonuclease resistance of at least twice that of a naturally occurring oligonucleotide having the same number of residues. --

-- 40. **[Amended]** The array of claim 34, wherein the modified oligonucleotides are further characterized by modification of at least 25% of their internucleoside linkages. --

-- 43. **[Amended]** The array of claim 34, wherein the nucleotide sequences of the oligonucleotides of an oligonucleotide composition on the array differs from those of the oligonucleotides of any other oligonucleotide composition on said array. --

Remarks

I. Status

Claims 34-46 have been examined. Applicant appreciates the assistance of the Examiner in reviewing the patentability of the present invention.

Applicant has amended the claims to more clearly describe Applicant's invention. Applicant has amended the claims to recite that the oligonucleotides of the claimed array have a length of from about 20 to about 300 nucleotides. Support for this recitation can be found in the specification at page 6, lines 18-20 (up to about 300 nucleotides), and page 38, line 2 (20 nucleotides). Applicant has additionally amended the claims to recite the nature of the internucleotide linkages of the recited oligonucleotides. Support for this

recitation can be found at page 13, lines 12-24. The remaining amendments have been made solely to remedy minor informalities or to address typographical or formatting errors. No new matter has been introduced by any of the requested amendments.

II. The Objection to the Specification

Applicant notes the maintenance of the Examiner's objection to the specification in light of the absence of a statement by Applicant's representatives that the paper and computer readable copies of the Sequence Listings are the same. Applicant respectfully submits that such a statement was believed to have been submitted with Applicant's Amendment of August 31, 2000. A copy of the previously submitted statement is enclosed. Applicant respectfully submits that the objection to the specification may now be properly withdrawn.

In the event that the submitted statement is insufficient, please contact the undersigned so that a new statement can be prepared and submitted.

III. The Rejections of the Claims

A. The Rejection of Claims 34 and 37-46 Under 35 U.S.C. § 103(a)

Claims 34 and 37-46 have been rejected as obvious over EP 0 742 287 A2 (McGall *et al.*), in light of WO 94/15619 (Miller *et al.*) and in view of US Patent No. 6,013,440 (Lipshutz *et al.*).

The Examiner has cited the McGall *et al.* document as disclosing arrays of oligonucleotides whose internucleotide linkages are modified at the 2' position. The Miller *et al.* document is cited as teaching that oligonucleotides having 2' methoxy groups are more stable than unmodified oligonucleotides to acid-induced degradation. The Lipshutz *et al.* document is cited as disclosing arrays of oligonucleotides in which the oligonucleotides are 150 nucleotides in length, and position in the array to as to create distinct areas having defined Tm intervals. The Examiner has suggested that those of

ordinary skill would have considered it obvious to have restricted the Tm range as taught the cited Lipshutz *et al.* document in forming the array as taught by the cited McGall *et al.* document because of the advantages of increased array specificity for target oligonucleotides, and the advantages of employing longer oligonucleotides stated to have been taught by the cited Lipshutz *et al.* document, and that such combined teachings would have rendered the presently claimed invention obvious. Applicant respectfully traverses and requests reconsideration.

As the Examiner has noted, those of ordinary skill in the art would not have found the cited McGall *et al.* document to disclose any acid-stabilizing value to employing 2' methoxy nucleotides, and would not have been motivated to prepare oligonucleotides whose substituents contain such groups in amounts sufficient to confer acid stability to the oligonucleotide. Applicant likewise agrees with the Examiner that the cited McGall *et al.* document additionally fails to disclose designing the array so that the associated oligonucleotides of one distinct area of the array exhibit substantially the same T_m when bound to a target nucleic acid as oligonucleotides of another distinct area of the array.

Applicant, however, respectfully directs the Examiner's attention to page 9, lines 34-35 of the cited McGall *et al.* document, wherein the authors disclose that the use of oligonucleotides of length greater than 15 would be disadvantageous. Applicant respectfully submits that the cited McGall *et al.* document would thus have taught away from the presently claimed invention, and would thus have failed to suggest Applicant's presently claimed invention. Applicant submits that this deficiency is not remedied by the secondary references cited by the Examiner. Although the cited Lipshutz *et al.* document discloses the use of oligonucleotide arrays in which the oligonucleotides are larger (preferably 150 nucleotides in length), the document provides no suggestion that such nucleotides should have 2' methoxy substituents. Accordingly, those of ordinary skill would have been motivated, if at all, only to replace short 2' methoxy-bearing

oligonucleotides (the cited McGall *et al.* document) with longer 2' OH- or H- bearing oligonucleotides (the cited Lipshutz *et al.* document).

Applicant moreover respectfully submits that the no motivation would have existed to employ non-methylphosphonate-containing oligonucleotides. Contrary to the suggestion raised by the Examiner, the cited Miller *et al.* document fails to provide *any* teaching relevant to the issue of the acid stability of oligonucleotides having 2'-O-alkyl groups – *but lacking methylphosphonate internucleotide linkages*. Applicant's review of the cited Miller *et al.* document has identified only data purporting to show the resistance to acidic degradation at pH 1of oligonucleotides containing methylphosphonate linkages.

In this regard, Applicant respectfully draws the Examiner's attention to the fact that the cited Miller *et al.* document *does* indeed report that the authors made oligonucleotides having 2'-O-alkyl groups but *lacking* methylphosphonate internucleotide linkages (see Example 5). However, *no* data concerning the alleged acid stability of this compound is presented. It is submitted that the failure of the cited Miller *et al.* document to present *any* data showing that such compounds are acid stable – *in a document otherwise concerned with the stability of modified oligonucleotides* – would have been interpreted by those of ordinary skill in the art as a statement that such molecules were *not* acid-stable in the absence of a methylphosphonate internucleotide backbone. As such, Applicant respectfully submits that the reference teaches away from the use of oligonucleotides having anything other than a methylphosphonate internucleotide linkage. Applicant thus submits that the cited Miller *et al.* document fails to suggest a modification of the arrays of the cited McGall *et al.* publication to contain non-methylphosphonate internucleotide linkages, and hence fails to detract from the patentability of the presently claimed invention.

Applicant accordingly submits that the rejection of claims 34 and 37-46 in light of the cited McGall *et al.*, Miller *et al.* and Lipshutz *et al.* documents may now be properly withdrawn.

B. The Rejection of Claims 35 and 36 Under 35 U.S.C. § 103(a)

Claims 35 and 36 have been rejected as obvious over EP 0 742 287 A2 (McGall *et al.*), in light of WO 94/15619 (Miller *et al.*) in view of US Patent No. 6,013,440 (Lipshutz *et al.*) further in view of US Patent No. 5,376,528 (King *et al.*). The cited King *et al.* patent is stated to describe the use of end-capped oligonucleotides, such that in combination with the art cited above, those of ordinary skill would have considered the inventions of claims 35 and 36 to have been obvious.

Applicant respectfully traverses and request reconsideration. Applicant respectfully submits that the cited King *et al.* patent does not suggest the use of end residues having 2' methoxy substituents, or the possibility that such residues could be bonded to the oligonucleotide by a non- non-methylphosphonate internucleotide linkage.

As discussed above, Applicant submits that the cited references primary references fail to suggest the presently claimed arrays in which oligonucleotides have 2'-methoxy substituents, and are selected to have substantially the same Tm when bound to a target nucleic acid, and lack methylphosphonate internucleotide linkages. Accordingly, Applicant submits the disclosure by King *et al.* of end-capping residues is insufficient to render the presently claimed invention obvious.

Applicant accordingly submits that the rejection of claims 34 and 37-46 in light of the cited McGall *et al.*, Miller *et al.*, Lipshutz *et al.*, and King *et al.* documents may be properly withdrawn.

Having now fully responded to all outstanding rejections, Applicant respectfully submits that the present application is in condition for Allowance, and earnestly solicit early notice of such favorable action. The Examiner is invited to contact the undersigned regarding any issue in this case.

Respectfully Submitted,

Date: 5/8/2001

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Appendix A: The Nature of the Requested Amendments

To facilitate the Examiner's review of the patentability of the present invention, Applicant has reproduced below the specific nature of the requested amendments.

34. **[Amended]** An array comprising:

(A) a support surface; and

(B) a plurality of modified oligonucleotide compositions, each composition comprising a plurality of oligonucleotides stably associated with a distinct area of the support surface, wherein the oligonucleotides of each composition are characterized by:

(1) **independently having a length of from about 20 to about 300 nucleotides;**

(2) **having internucleotide linkages selected from the group consisting of phosphorothioate linkages, 2'-O-methyl-phosphodiesters, 2'-O-alkyl, 2'-O-ethyl, 2'-O-propyl, 2'-O-butyl, 2'-O-alkyl-n(O-alkyl), 2'-methoxyethoxy, 2'-fluoro, 2'-deoxy-erythropentofuranosyl, 3'-O-methyl, p-isopropyl oligonucleotides, phosphodiester, 2'-O(CH2CH2O)$_x$CH3, butyne, phosphotriester, phosphoramidate, propargyl, siloxane, carbonate, carboxymethylester, methoxyethoxy, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, phosphorodithioate, bridged phosphorothioate and/or sulfone internucleotide linkages, 3'-3', 5'-5', 5'-2' linkages, and combinations thereof;**

(3) **having** a binding affinity to a complementary sequence greater than the corresponding binding affinity of a non-modified oligonucleotide having the same sequence;

(4) **having nucleotides that possess** a substitution at a 2' position of the ribose group, said substitution distinguishing said oligonucleotide from naturally occurring RNA or DNA; and

(5) **having** a pH stability of at least one hour at 37°C at a pH in a range of about 0.5 to 6;

wherein the associated oligonucleotides of one distinct area of the array exhibit substantially the same T_m when bound to a target nucleic acid as oligonucleotides of another distinct area of the array.

35. **[Amended]** The array of claim 34, wherein the modified oligonucleotides further comprise an end block at the 3' end and **exhibit** exonuclease resistance of at least twice that of a naturally occurring oligonucleotide having the same number of residues.

36. **[Amended]** The array of claim 34, wherein the modified oligonucleotides further comprise an end block at the 5' end and **exhibit** exonuclease resistance of at least twice that of a naturally occurring oligonucleotide having the same number of residues.

37. The array of claim 34, wherein the modified oligonucleotides of each distinct area of the array exhibit substantially the same T_m.

38. The array of claim 34, wherein the modified oligonucleotides of a distinct area are selectively designed to hybridize to RNA.

39. The array of claim 34, wherein the modified oligonucleotides of a distinct area are selectively designed to hybridize to DNA.

40. **[Amended]** The array of claim 34, wherein the modified oligonucleotide**s** [is] **are** further characterized by modification of at least 25% of the**ir** internucleoside linkages [of the oligonucleotide].

41. **[Cancelled]** The array of claim 34, wherein said modified oligonucleotides have an average length of from about 80 to about 300 nucleotides.

42. The array of claim 34, wherein said modified oligonucleotides have an average length of from about 100 to about 200 nucleotides.

43. **[Amended]** The array of claim 34, wherein **the nucleotide sequences of the** oligonucleotides of **an** [each of said] oligonucleotide composition[s has a different] **on the array differs from those** [sequence from] **of the** oligonucleotides of any other oligonucleotide composition on [the] **said** array.

44. The array of claim 34, wherein each oligonucleotide composition comprises a population of identical oligonucleotides.

45. The array of claim 34, wherein each oligonucleotide composition comprises a plurality of oligonucleotides that bind to a particular nucleic acid.

46. The array of claim 34, wherein the number of oligonucleotide compositions on said array ranges from about 2 to about 10^9.

Appendix B: The Pending Claims

To facilitate the Examiner's review of the patentability of the present invention, Applicant has reproduced below the pending claims.

34. **[Amended]** An array comprising:

(A) a support surface; and

(B) a plurality of modified oligonucleotide compositions, each composition comprising a plurality of oligonucleotides stably associated with a distinct area of the support surface, wherein the oligonucleotides of each composition are characterized by:

(1) independently having a length of from about 20 to about 300 nucleotides;

(2) having internucleotide linkages selected from the group consisting of phosphorothioate linkages, 2'-O-methyl-phosphodiesters, 2'-O-alkyl, 2'-O-ethyl, 2'-O-propyl, 2'-O-butyl, 2'-O-alkyl-n(O-alkyl), 2'-methoxyethoxy, 2'-fluoro, 2'-deoxy-erythropentofuranosyl, 3'-O-methyl, p-isopropyl oligonucleotides, phosphodiester, 2'-$O(CH2CH2O)_xCH3$, butyne, phosphotriester, phosphoramidate, propargyl, siloxane, carbonate, carboxymethylester, methoxyethoxy, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, phosphorodithioate, bridged phosphorothioate and/or sulfone internucleotide linkages, 3'-3', 5'-5', 5'-2' linkages, and combinations thereof;

(3) having a binding affinity to a complementary sequence greater than the corresponding binding affinity of a non-modified oligonucleotide having the same sequence;

(4) having nucleotides that possess a substitution at a 2' position of the ribose group, said substitution distinguishing said oligonucleotide from naturally occurring RNA or DNA; and

(5) having a pH stability of at least one hour at 37°C at a pH in a range of about 0.5 to 6;

wherein the associated oligonucleotides of one distinct area of the array exhibit substantially the same T_m when bound to a target nucleic acid as oligonucleotides of another distinct area of the array.

35. **[Amended]** The array of claim 34, wherein the modified oligonucleotides further comprise an end block at the 3' end and exhibit exonuclease resistance of at least twice that of a naturally occurring oligonucleotide having the same number of residues.

36. **[Amended]** The array of claim 34, wherein the modified oligonucleotides further comprise an end block at the 5' end and exhibit exonuclease resistance of at least twice that of a naturally occurring oligonucleotide having the same number of residues.

37. The array of claim 34, wherein the modified oligonucleotides of each distinct area of the array exhibit substantially the same T_m.

38. The array of claim 34, wherein the modified oligonucleotides of a distinct area are selectively designed to hybridize to RNA.

39. The array of claim 34, wherein the modified oligonucleotides of a distinct area are selectively designed to hybridize to DNA.

40. **[Amended]** The array of claim 34, wherein the modified oligonucleotides are further characterized by modification of at least 25% of their internucleoside linkages.

42. The array of claim 34, wherein said modified oligonucleotides have an average length of from about 100 to about 200 nucleotides.

43. **[Amended]** The array of claim 34, wherein the nucleotide sequences of the oligonucleotides of an oligonucleotide composition on the array differs from those of the oligonucleotides of any other oligonucleotide composition on said array.

44. The array of claim 34, wherein each oligonucleotide composition comprises a population of identical oligonucleotides.

45. The array of claim 34, wherein each oligonucleotide composition comprises a plurality of oligonucleotides that bind to a particular nucleic acid.

46. The array of claim 34, wherein the number of oligonucleotide compositions on said array ranges from about 2 to about 10^9.